## REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

In the present Office Action, Claims 16-23 stand rejected under 35 U.S.C. §101 as allegedly improper. Specifically, the Examiner asserts that Claims 16-23 are directed to a use, but there are no steps recited therein. Furthermore, Claims 16-23 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the same reasons as discussed in the above.

In response, applicants have deleted Claims 16-23 without prejudice. Moreover, applicants have added new Claims 28-30 where the subject matter recited therein are covered by deleted Claims 21 and 22. Support for the new Claims 28-30 can be found at Page 9, lines 1-8, for example.

Since the above amendments to the claims do not introduce any new matter into the application, entry thereof is respectfully requested. Moreover, since the amendments to Claims 16-23 obviate the §101 rejection and the §112, second paragraph rejection, reconsideration and withdrawal of the instant rejections are respectfully requested.

Furthermore, Claims 1-7, 9-14, 16-19 and 21-27 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, Claims 1 and 9 are rejected in view of the expression "distamycin or distamycin-like framework." The Examiner avers that such expression is too broad. As far as Claims 9-15 are concerned, they are rejected in view of the term "products." The Examiner asserts that such term embraces more than a single product, and it is unclear whether applicants claim each product individually or as a group. Furthermore, the Examiner avers that the expression "as a combined preparation for simultaneous, separate or sequential use" renders Claim 9 vague and indefinite.

In response, with respect to the rejection to Claims 1 and 9 based upon the expression "distamycin or distamycin-like framework," applicants have amended Claims 1 and 9 by introducing the meaning of $R_2$, presently appearing in original Claims 4 and Claim 12, into Claim 1 and 9 respectively. Applicants have also deleted original Claim 4. Support for the above-mentioned amendment can be found at 3, line 14 to Page 4, line 16.

Moreover, in response to the rejection to Claims 9-15 regarding the term "products", applicants have amended such term to the singular "product" in Claims 9-15. Support for the above-mentioned amendment can be found at Page 7, line 18 where it describes that "[t]he present invention further provides a product, otherwise referred to as kit of parts."

Since the above amendments to the claims do not introduce any new matter into the application, entry thereof is respectfully requested.

With respect to the rejection to Claim 9 based upon the expression "as a combined preparation for simultaneous, separate or sequential use", it appears that the Examiner is under the impression that a composition implies that the components are intimately mixed and that the recitation of separate or sequential use is contrary to the ordinary definition of a pharmaceutical composition.

In response, applicants submit that Claim 9 is directed to a product, rather than to a composition. While it is true that a pharmaceutical composition includes a single product that combines components recited therein, a product clearly infers separate and distinct components. Furthermore, applicants submit that claims must be interpreted in light of the specification. The instant specification (page 8, lines 8-10) describes that "[i]n the method of the present invention, the acryloyl distamycin derivative may be administered simultaneously with the PK inhibitor or, alternatively, both compounds may be administered sequentially in either order." In view of the

above plain language, the term "combined preparation" means the treatment is staged, rather than combining the two drugs into one drug.

In view of the above-mentioned amendments to Claims 1 and 9-15, and the above remarks, applicants submit that the instant §112, second paragraph rejection is obviated, therefore, reconsideration and withdrawal of the instant rejections are respectfully requested.

In addition to the above-mentioned formal ground rejections, Claims 1-27 stand rejected under 35 U.S.C. §103(a) as obvious over Cozzi et al.(WO 98/04525) in view of Sironak et al. (Clinical Cancer Research: 2000, 6(12); 4885-4892) and further in view of Grimley et al. (US 6,274,576). Specifically, the Examiner asserts that Cozzi et al. teach the acryloyl distamycin derivative of formula (I), and further teach that such derivative can be combined with an additional antitumor agent for treating cancer. The Examiner expressly admits that Cozzi et al. does not teach using a protein kinase inhibitor (PKI) to treat cancer or the inhibitor itself. With respect to Sironal et al., the Examiner asserts that it teaches that ZD 1839, a PKI, can be combined with other cancer-treating agents. Regarding Grimley et al., the Examiner alleges that it teaches a combination of cell killing agents, including PKI, can be used in cancer chemotherapy to achieve better treatment on target cells, while minimize the toxic effect on non-target cells. Therefore, the Examiner alleges that it would be obvious for a person skilled in the art to combine the compounds taught by Cozzi et al., with a PKI taught by Sironak et al. in a cancer treatment to achieve better results. The Examiner further asserts that such combined treatment is prima facie obvious; each of the composition components is taught in the prior art to be useful for the same purpose in order to form a third composition that is to be used for the same purpose. Furthermore, with respect to Claim 26, which is directed to a method of lowering side effects caused by cancer treatment, the Examiner alleges that it would be obvious for a

person skilled in the art that the combination of an acryloyl distamycin derivative of formula (I) and PKI would produce synergistic effects and thus reduce the side-effects of such treatment, since this is taught by Grimley et al. and can even be considered as common knowledge of the skilled artisan.

In response, applicants have amended Claim 1 to include the term "having a synergistic antineoplastic effect." Support for the above-mentioned amendment can be found at Page 1, lines 5-9. In view of the above-described amendment, applicants submit that the present invention is not obvious over the cited references, since those references, either alone in combination, do not teach, disclose or suggest applicant's claimed composition, product and method of treatment.

Specifically, with respect to Cozzi et al., applicants submit that there are several differences between the composition in Cozzi et al. and that of the present invention. First, Cozzi et al. teach that an acryloyl distamycin compound may be combined with an antitumor agent, but it does not teach that a α-bromo or α-chloro- acryloyl distamycin compound of formula (I) can be combined with a protein kinase inhibitor, which is in accordance with the present invention. It is to be noted that the scope of acryloyl distamycin compound disclosed in Cozzi et al. is somewhat broader than that of formula (I) of the present invention with respect to the substituents on the acryloyl group. Specifically, $R_1$ and $R_2$ in formula (I) of Cozzi et al. can be hydrogen, halogen, and $C_1$-$C_4$ alkyl, while the corresponding substituents in formula (I) of the present invention are both hydrogen. Second, Cozzi et al. teaches, in general terms and without providing any substantive evidence, that an acryloyl distamycin compound may be used in combination with additional antitumor agent in the treatment of cancer, but it does not teach, disclose or suggest that an antitumor composition comprising an α-bromo or α-chloro- acryloyl

distamycin compound of formula (I) and a protein kinase inhibitor having a synergistic antineoplastic effect. Thus, applicants submit that the present composition, the product and the method of treatment based upon such composition is not obvious to a person skilled in the art from the teaching of Cozzi et al.

With respect to the secondary reference, Sironak et al. discloses a combined use of ZD 1839, a protein kinase inhibitor, with a cytotoxic compound, i.e., gemcitabine(GEM), edatrexate (10-ethyl-deazaaminopterin) (EDX), paclitaxel (PTXL), docetaxel (DTXL), vinorelbine (VNR), cisplatin (CDDP), carboplatinum (CBDCA) and doxorubicin (DOX), respectively. It is to be noted that the above-identified cytotoxic compounds disclosed in Sironak et al., are structurally and functionally different from acryloyl distamycin derivatives of the present invention.

It is well known in the cancer research filed that the effectiveness of a therapeutic treatment is dependent upon the chemical structure of the compound and the function of the compound in its mechanism of action with the biological target. If the structure and the function of the compounds are different from one art to another, one would be unable to utilize the same methodology as in the prior art to effect the therapeutic treatment. There is no way of predicting that the class of compounds used in the prior art could also be used in another prior art, or in the present invention. The type of methodology utilized is dependent upon each set of circumstances and cannot be generalized. This principle is further supported by the disclosure of Sironak et al. itself because the cited reference states how ZD 1839 enhances the antitumor activity of a number of cytotoxic agents and that this enhancement involves highly diverse mechanisms of action (see page 4890, the first three lines of the last paragraph on the right column). The cited reference further states that GEM and VNR, with different structures and

functions from the other five compounds, either shows no enhanced antitumor activities or confers exceedingly high toxicity respectively, when combined with ZD 1839 (see Page 4886, the first paragraph in the left column).

Applicants would like to draw the Examiner's attention to the fact that the structure and function of compounds in the primary reference are different from that of the secondary reference, therefore a person skilled in the art would not combine the two references in the first instance. Even combining the two cited references, the combined teachings do not overcome the deficiencies of the primary reference, since Sironak et al. do not teach, disclose or suggest the combination of an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I) with a protein kinase inhibitor can produce a synergistic antineoplastic effect.

With respect to the other secondary reference, Grimley et al. teach a method of potentiating cell damage by administering a restraining agent and a targeted cytotoxic insult wherein the function of the restraining agent is to retard but not arrest downstream progress of a target cell population through the cell cycle (see Column 15, lines 60-66).

Although Grimley et al. may disclose that the restraining agent can be PKI, it is to be noted that the targeted cytotoxic insult disclosed therein is indole carbazoles (see Column 15, lines 30-32), whose structure and function are totally different from that of the compounds in the primary and other secondary references. Therefore, for the same reason as explained above, a person skilled in the art would not combine Grimley et al. with the other two cited references in the first instance. Moreover, Grimley et al. does not teach, disclose or suggest that the combination of restraining agents or targeted cytotoxic insults with an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I) can produce a synergistic antineoplastic effect. Even combining Grimley et al. with other two cited references, the combined teachings do not

overcome the deficiencies of the primary reference, since Grimley et al. do not teach, disclose or suggest the combination of an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I) with a protein kinase inhibitor can produce a synergistic antineoplastic effect. Furthermore, even assuming the disclosures in the cited references present a prima facie case of obviousness, that case can be rebutted by a showing of unexpected results. To that end, applicants submit additional in vitro data (enclosed as Exhibit 1) regarding the combination of brostallicin (an α-bromo- or α-chloro-acryloyl-distamycin derivative of formula (I)) with ST1571 (a protein kinase inhibitor) on K562 human CML cell line, ZD1839 (a protein kinase inhibitor) on human lung cancer NCI-H322M human lung cancer cell line, and OSI-774 (a protein kinase inhibitor) on MDA-MB-468 human breast carcinoma cell line respectively. The above-mentioned in vitro data shows that, on human tumor cells, brostallicin can be combined effectively with each of the above-identified three protein kinase inhibitors to produce a synergistic effect. The above unexpected and superior biological data further strengthen applicants' position that the present invention is non-obvious over the teachings of the cited references.

In view of the above remarks, applicants respectfully submit that Claims 1-27 are not rendered obvious over all the cited references. As such, reconsideration and withdrawal of the instant rejection is respectfully requested.

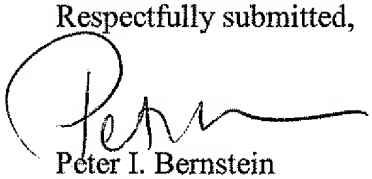
Furthermore, Claims 1-27 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 of U.S. Patent No. 6,482,920 ('920) in view of Sironak et al.

Applicants observe that the '920 patent is derived from Cozzi et al. which is discussed in the above. Therefore, applicants submit that the above remarks concerning the

obviousness type rejection over Claim 1-27 in view of Cozzi et al. and Sironak et al. apply equally well to this rejection, and therefore are incorporated herein. As such, applicants submit that Claims 1-27 are not obvious over the cited references and reconsideration and withdrawal of the instant rejection is respectfully requested.

In view of foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Enclosure : Exhibit 1

EXHIBIT 1

IN VITRO CYTOTOXIC ACTIVITY

Exponentially growing cells were seeded and incubated at 37°C in a humidified 5% $CO_2$ atmosphere. After 24 hours, scalar doses of brostallicin plus the kinase inhibitor were added to the medium and cells were treated for 72 hours. At the end of treatment, cell proliferation was determined by a cellular adenosine triphosphate monitoring system. Cell proliferation was compared to control cells. All tested cell lines were sensitive to brostallicin. For each combination, the cell line most sensitive to the kinase inhibitor was selected: human CML K562 (BCR-ABL positive) for STI571 (Gleevec); human lung cancer NCI-H322M for ZD1839 (Iressa) and human breast cancer MDA-MB-468 for OSI-774 (Tarceva).

The combination indices (C.I.) were calculated using a computer program for multiple drug effect analysis based on the equation of Chou-Talalay (Adv Enzyme Regul 1984;22:27–55) for mutually nonexclusive drugs, where a C.I. of <1 in vitro indicates a more than additive effect.

The results obtained with the drugs as single agents and in combination are shown in tables 1-3.

Table 1: in vitro combination of brostallicin with STI571 on K562 human CML cell line

| | $IC_{50}$ (μM) | C.I.<br>At 90% of fraction affected |
|---|---|---|
| Brostallicin | 0.304 | |
| STI571 | 0.348 | |
| Combination (ratio 1:1)<br>Brostallicin<br>STI571 | <br>0.218<br>0.218 | 0.69 |

Table 2: in vitro combination of brostallicin with ZD1839 on human lung cancer NCI-H322M human lung cancer cell line

| | $IC_{50}$ (μM) | C.I. At 90% of fraction affected |
|---|---|---|
| Brostallicin | 0.249 | |
| ZD1839 | 0.494 | |
| Combination (ratio 1 : 1.25)<br>Brostallicin<br>ZD1839 | <br>0.178<br>0.222 | **0.62** |

Table 3: in vitro combination of brostallicin with OSI-774 on MDA-MB-468 human breast carcinoma cell line

| | $IC_{50}$ (μM) | C.I. At 90% of fraction affected |
|---|---|---|
| Brostallicin | 0.0014 | |
| OSI-774 | 1.076 | |
| Combination (ratio 1: 250)<br>Brostallicin<br>OSI-774 | <br>0.0036<br>0.891 | **0.67** |

The results show that on human tumor cells brostallicin can be combined effectively with STI571 (Gleevec), ZD1839 (Iressa) or OSI-774 (Tarceva) producing a more than additive (i.e. synergic) effect.